Journal of Clinical Investigation
Vol. 42, No. 5, 1963

BRISKET DISEASE. III. SPONTANEOUS REMISSION OF PULMONARY HYPERTENSION AND RECOVERY FROM HEART FAILURE *

BY HIROSHI KUIDA, HANS H. HECHT, RAMON L. LANGE,† ARTHUR M. BROWN,‡ THEOFILOS J. TSAGARIS, AND JOSEPH L. THORNE

(*From the Department of Internal Medicine, University of Utah College of Medicine, Salt Lake City, Utah*)

(Submitted for publication August 11, 1962; accepted January 3, 1963)

Previous reports from this laboratory have dealt with the ecologic, pathologic, clinical, and pathophysiologic features of brisket disease (1, 2). On the basis of these studies brisket disease may be defined as altitude-dependent, pulmonary, hypertensive heart disease in cattle of the species *Bos taurus*. Briefly, the disease in Utah occurs primarily in young calves usually during their first exposure to conditions existing on summer ranges at elevations between 8,000 and 11,000 feet. Typical findings in animals suffering from brisket disease are outlined in Table I.

It was observed that a significant number of animals with acute brisket disease recovered when removed from the mountainous ranges and brought to Salt Lake City, Utah (elevation 4,500 feet). This observation prompted an investigation of the nature, magnitude, and time course of changes in various physiologic parameters associated with clinical recovery. The demonstration of dramatic remission from pulmonary hypertension and improvement in over-all cardiovascular function provides the basis for this report.

METHOD

Over a period of 4 years, 43 venous and 21 left ventricular cardiac catheterization studies were carried out in 14 animals that recovered from brisket disease. These calves were among a group of 42 in which hemodynamic observations were made during acute brisket disease. Five animals were studied twice, six were studied three times, and four separate observations were made on the remaining three. The initial catheterization procedure in each animal was performed during the acute phase of brisket disease within a few days of arrival in Salt Lake City.

The interval between the first and last observation ranged from 1 to 7 months and averaged 11 weeks. The shortest interval between two successive studies in one animal was 4 days and the longest, 108 days. Three of the 43 studies were carried out in three animals of a group of five that were re-exposed to the high altitude range during the grazing season succeeding the one during which brisket disease had developed. These are considered neither acute nor recovery studies and are not included in the analysis of data. The time course of changes associated with recovery was examined in six animals that were studied a total of 19 times. In this group the interval between successive observations ranged from 4 to 46 days and averaged 19 days.

All procedures were conducted in the cardiovascular research laboratory. Except during these procedures, animals were kept in a nearby stock yard or on a farm. Additional dietary salt was withheld as a matter of routine, but animals were permitted free access to water. Three calves were given digitalis and a mercurial diuretic parentally for short periods during the acute phase of heart failure. None of these calves was included in the "time course" study.

The methods used in performing cardiac catheterization and obtaining measurements of various hemodynamic parameters are described in detail elsewhere (3). Half-way through the present investigation the use of promazine hydrochloride in an attempt to obtain tranquility in the animals was discontinued. The drug appeared to have little effect in the doses used. Furthermore, a similar drug

TABLE I

Characteristic clinical features of brisket disease

1. Progressive limitation in exertional tolerance
   a. Reluctance to move when herded
   b. Labored breathing
   c. Easy fatigability
2. Decelerated growth and weight gain
3. Diarrhea (scours)
4. Droopy ears
5. Distended, pulsating external jugular veins
6. Accentuated second heart sound (P_2)
7. Pansystolic, blowing heart murmur*
8. Gallop rhythm*
9. Edema of brisket*

* Not invariably present.

* This study was supported in part by grants from the Utah Heart Association, the U. S. Public Health Service (H-4299 and HTS-5150), and the American Heart Association.

† Present address: Department of Internal Medicine, Marquette University School of Medicine, Milwaukee, Wis.

‡ Department of Physiology, University of London, Middlesex Hospital Medical School, London, England.

TABLE II

*Statistical analysis of changes in several hemodynamic parameters associated with recovery from brisket disease (BD)**

Parameter	Acute BD† Mean ± SE	Recovery‡ Mean ± SE	Δ§ Mean ± SE	p‖
Weight, *kg*	116 ± 10.4	143 ± 11.8	+26.7 ± 9.8	<0.02
Body surface area, m^2	2.12 ± 0.11	2.38 ± 0.12	+0.27 ± 0.09	<0.02
VPRC, %	44.5 ± 1.6	38.8 ± 1.6	−5.6 ± 1.4	<0.01
Hemoglobin, *g %*	13.7 ± 0.7	11.8 ± 0.5	−1.94 ± 0.5	<0.01
Sa_{O_2}, %	82.5 ± 3.1	91.5 ± 1.2	+9.1 ± 3.3	<0.02
$C\bar{v}_{O_2}$, *vol %*	8.63 ± 1.08	9.51 ± 0.70	+0.88 ± 1.01	>0.3
$S\bar{v}_{O_2}$, %	47.5 ± 5.0	61 ± 1.75	+14.3 ± 4.54	<0.01
$Ca\bar{v}_{O_2}$, *vol %*	6.00 ± 0.51	4.50 ± 0.36	−1.50 ± 0.52	<0.02
pH¶	7.39 ± 0.01	7.41 ± 0.01		>0.20
C.I., *L/min/m²*	4.92 ± 0.59	6.08 ± 0.51	+1.16 ± 0.77	>0.10
Mean pressures, *mm Hg*				
Pulmonary artery	63.4 ± 5.86	31.8 ± 2.67	−36 ± 5.5	<0.01
Systemic artery	109 ± 8.3	128 ± 6.0	+13 ± 10	>0.20
Right atrium	21.2 ± 3.8	+0.3 ± 1.0	−20.9 ± 3.4	<0.01
PA wedge	23.2 ± 2.7	11.6 ± 2.5	−10.6 ± 3.7	<0.05
PVRI, *mm Hg/L/min/m²*	12.34 ± 2.17	3.84 ± 0.40	−8.43 ± 2.22	<0.01

* Abbreviations: VPRC = volume of packed red cells; Sa_{O_2}, $S\bar{v}_{O_2}$ = arterial and mixed venous blood hemoglobin saturation; $C\bar{v}_{O_2}$ = mixed venous blood oxygen content; $Ca\bar{v}_{O_2}$ = arteriovenous oxygen difference; *C.I.* = cardiac index; *PVRI* = calculated pulmonary vascular resistance index.

† Obtained from analysis of data from first study in each animal.

‡ Obtained from analysis of data from last study in each animal.

§ Difference between acute brisket and recovery data in each animal; positive values are indicative of an increase and negative values a decrease in the parameter associated with recovery.

‖ Values less than 0.05 are considered to indicate a statistically significant difference between acute and recovery data.

¶ pH values converted to hydrogen ion concentration for statistical analysis.

has been reported to produce significant hemodynamic alterations, at least at a dose level approximately double those used here (4). Each study required that a separate cutdown be made over the left external jugular vein for the exposure of this vessel and the left carotid artery. Holes made in the walls of these vessels for catheter insertion were repaired at the termination of each procedure, thus permitting their reuse during subsequent studies.

Pulmonary vascular resistance index (*PVRI*) was calculated from the following formula:

$$PVRI\ (\text{mm Hg/L/min/m}^2) = \frac{\overline{PA} - \overline{PA}_w \text{ or } LV_{ed}}{C.I.},$$

where $\overline{PA}$ = mean pulmonary artery pressure in millimeters of Hg, $\overline{PA}_w$ = mean pulmonary artery wedge pressure in millimeters of Hg, LV_{ed} = left ventricular end-diastolic pressure in millimeters of Hg, and *C.I.* = cardiac index in liters per minute per meter squared of body surface area (BSA). BSA was calculated from: BSA = 0.15 kg (body weight)$^{0.56}$ (5). In the five studies on the first three animals in this series neither PA_w nor LV_{ed} was obtained. Thus, in the calculation of *PVRI* in these studies a value of 20 mm Hg was assumed for the acute phase and 5 mm Hg for the recovery (2). Minute work of the right (W_{RV}) and left (W_{LV}) ventricles was calculated by the formulas:

$$W_{RV}\ (\text{kg-m/min/m}^2) = K \times C.I.\ (\overline{PA} - RV_{ed})$$

and

$$W_{LV}\ (\text{kg-m/min/m}^2) = K \times C.I.\ (\overline{Ao} - LV_{ed}),$$

where K = a constant (0.01435) which provides conversion of liters of blood times millimeters of Hg to work units (kilogram-meters of water); RV_{ed} = right ventricular end-diastolic pressure in mm Hg; and $\overline{Ao}$ = mean aortic pressure in mm Hg.

Procedures other than those pertaining to this study were carried out in some of these animals during either the acute or recovery phase. For this reason, only the initial "resting" measurements of the various parameters during each study were used in the analysis of data. In most instances, paired resting observations were made and in these cases an average value was taken.

Mean and standard error of the mean were calculated for the acute and recovery data by standard statistical formulas. The mean difference and standard error of the mean difference were obtained by the pairing design test wherein the differences between acute and recovery observations in each animal were analyzed.

RESULTS

All clinical manifestations of brisket disease listed in Table I disappeared usually within the first 4 to 6 weeks. Changes in various hemodynamic parameters associated with recovery are shown in Table II. The recovery data in this table were obtained from analysis of only the last study in each animal.

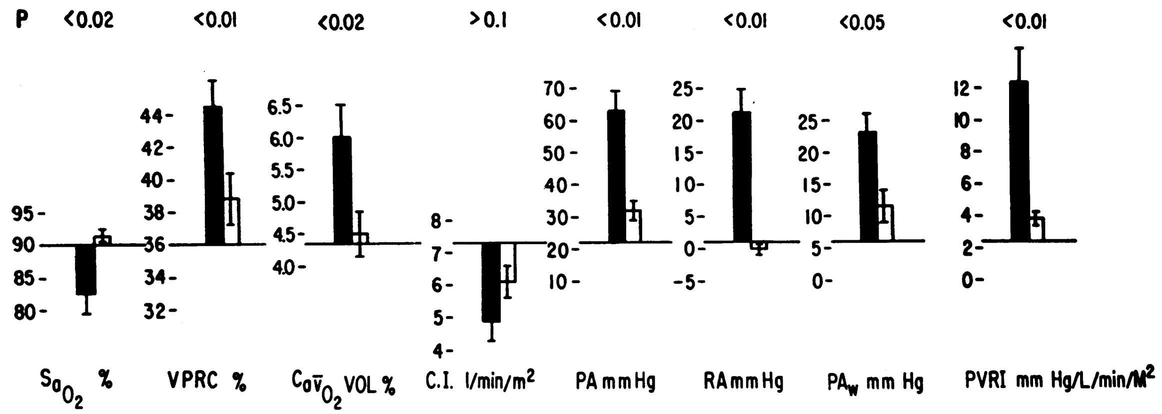

FIG. 1. MEAN ± SE VALUES OF VARIOUS PHYSIOLOGIC PARAMETERS IN 14 ANIMALS DURING ACUTE BRISKET DISEASE (SOLID BARS) COMPARED WITH VALUES IN THESE ANIMALS AFTER RECOVERY (OPEN BARS). The reference level (horizontal line) provides the average value of each parameter obtained in 15 normal (control) animals. The 5% level ($p < 0.05$) was selected to determine significant differences between acute and recovery data. Sa_{O_2} = oxyhemoglobin saturation in arterial blood; VPRC = volume of packed red cells; $Ca\bar{v}_{O_2}$ = oxygen content difference between arterial and mixed venous blood; *C.I.* = cardiac index; *PA*, *RA*, PA_w = pressures in pulmonary artery, right atrium, and pulmonary artery wedge, respectively; *PVRI* = calculated pulmonary vascular resistance index.

The increase in weight (mean 27 kg) associated with a period for potential growth averaging 3 months is misleading in that body weights during the acute study were undoubtedly distorted by the presence of congestive heart failure. Indeed, in a few animals that were weighed more frequently after the acute study, it was noted that weight loss of 7 to 15% (average 13 kg) of the initial weight took place during the first 2 weeks. This weight loss presumably was related to a loss

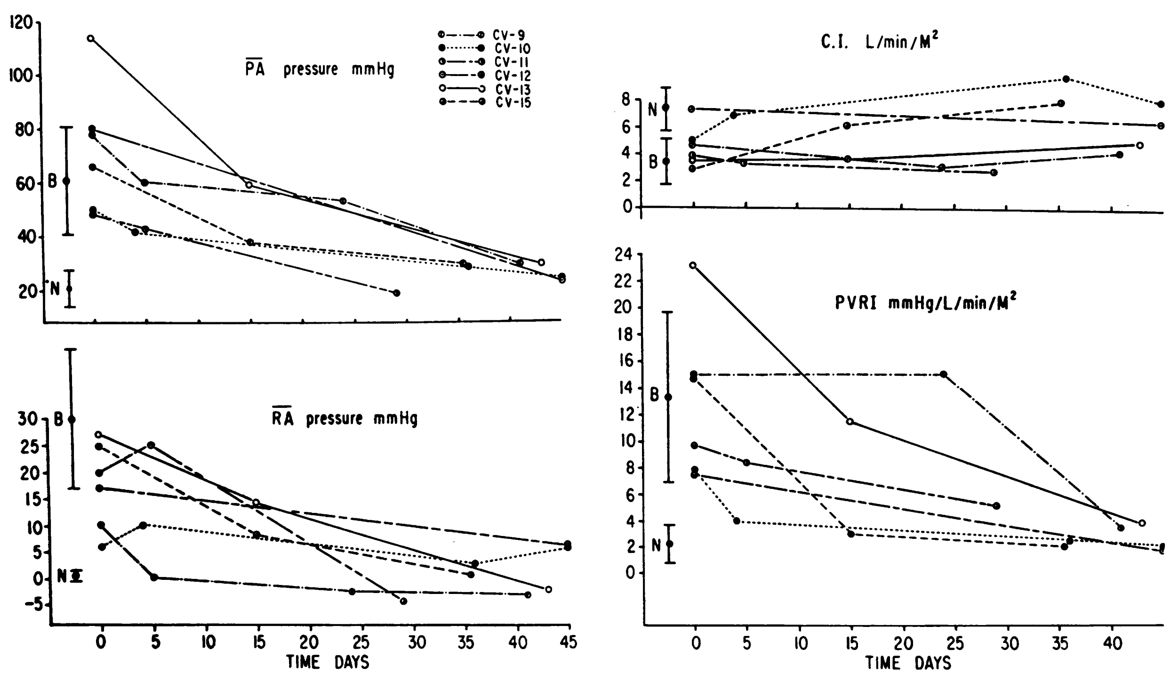

FIG. 2. TIME COURSE OF CHANGES IN FOUR PARAMETERS IN SIX ANIMALS STUDIED 19 TIMES. Mean ± SD values for each parameter in normal (N) and acute brisket disease (B) animals were obtained from references 3 and 2, respectively.

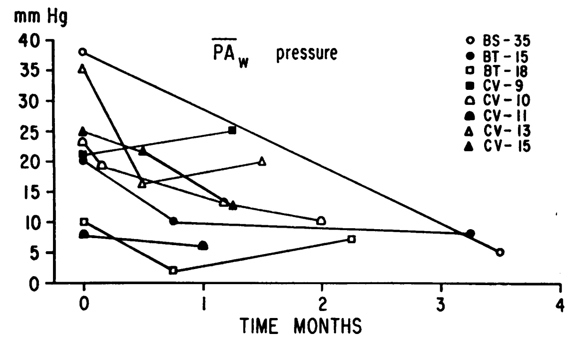

FIG. 3. CHANGES IN MEAN PULMONARY ARTERY WEDGE ($\overline{PA}_w$) PRESSURE ASSOCIATED WITH TIME IN EIGHT ANIMALS.

of body water (diuresis). Although mixed venous blood oxygen content ($C\bar{v}_{O_2}$) did not change significantly (p = > 0.3) with recovery, the fact that average oxygen capacity (hemoglobin content) fell and cardiac output rose at the same time provides the explanation for the significant (p = < 0.01) improvement in mixed venous oxygen saturation ($S\bar{v}_{O_2}$). It is apparent, also, that $C\bar{v}_{O_2}$ increased more than arterial blood oxygen content (Ca_{O_2}) as the net oxygen content difference between arterial and mixed venous blood ($Ca\bar{v}_{O_2}$) narrowed, presumably in relation to the improvement in cardiac output.

The alterations in parameters selected because of their particular interest to us are shown diagrammatically in Figure 1. The mean value of each parameter during the acute phase and after recovery is shown as a deviation (in absolute units) from the mean normal value for that parameter obtained in 15 control animals reported previously (3). This figure demonstrates that in association with recovery normality was approached but not completely achieved.

The time course of recovery in six animals as measured by regression of certain physiologic abnormalities is demonstrated in Figure 2. It may be seen that the remission rate is relatively rapid, recovery being virtually complete after only 6 weeks. A similar decline in mean $\overline{PA}_w$ pressure in 6 of 8 animals is shown in Figure 3.

In Figure 4 are shown the results of restudy of three animals in a group of five that were re-exposed to the same ranges at high altitude on which they developed brisket disease initially. There was a recurrence of the typical clinical manifestations of the disease in only one of the five calves. This animal (BS-58) was brought back to Salt Lake City after 4 weeks at 9,000 feet, and restudy demonstrated characteristic and severe physiologic abnormalities. On the other hand, restudy of two (BS-35 and BS-52) of the four animals that did not have a clinical recurrence after 8 weeks at the same altitude showed essentially normal findings.

Changes in right and left ventricular performance associated with recovery as measured by the relationship of cardiac minute work to ventricular end-diastolic (filling) pressure are shown in Figure 5. It should be noted that right ventricular work in some animals represents only

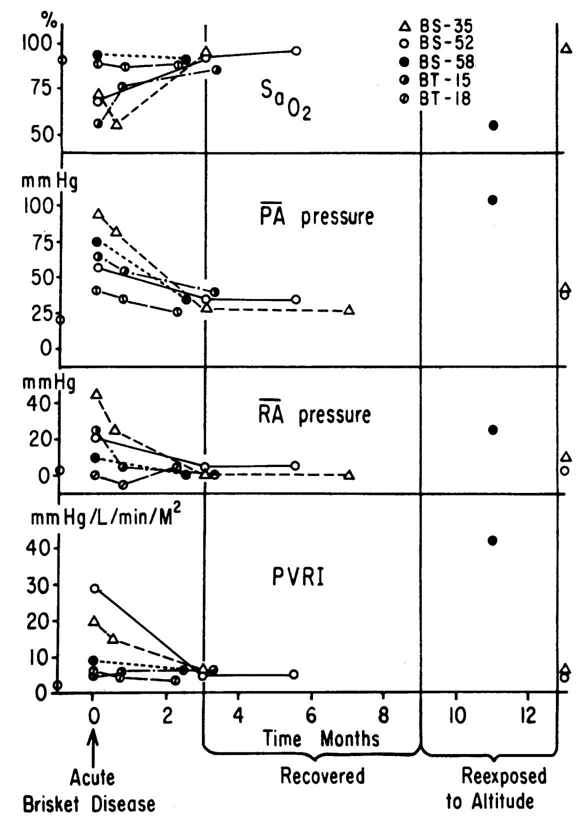

FIG. 4. SERIAL STUDIES IN FIVE ANIMALS THAT RECOVERED FROM ACUTE BRISKET DISEASE (LEFT SIDE OF FIGURE). Three of the five calves returned to high altitude were subsequently restudied at the times indicated (right side of figure). Only one animal (BS-58) redeveloped the typical manifestations of brisket disease and when studied had characteristic physiologic abnormalities. Studies in two of the four animals that did not redevelop brisket disease were essentially normal. The circles on the ordinate of the graphs of each parameter represent mean values in normal animals.

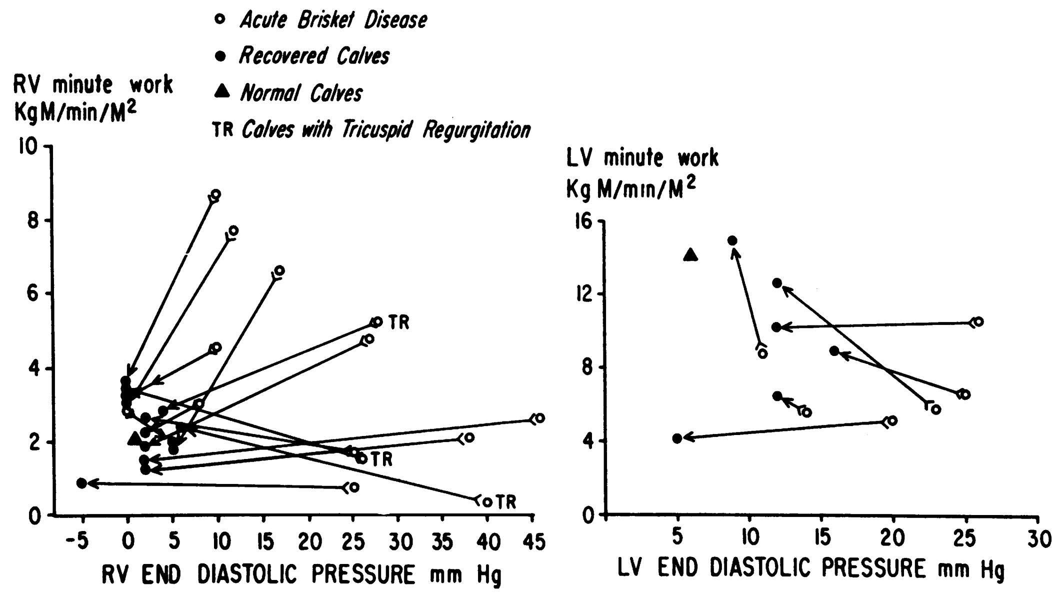

FIG. 5. RELATIONSHIP OF RIGHT (RV) AND LEFT (LV) VENTRICULAR MINUTE WORK TO END-DIASTOLIC PRESSURE DURING ACUTE BRISKET DISEASE AND AFTER RECOVERY. Changes in each animal are indicated by an arrow connecting the two points. The relationship between these parameters in normal animals is shown by the triangle. Improvement in ventricular performance may be inferred in instances where there is a marked decrease in end-diastolic pressure associated with a slight decrease, no change, or increase in ventricular work.

effective or "forward" work and not total right ventricular work because of the actual or potential existence of tricuspid regurgitation (2). The regurgitant flow was not quantitated and, therefore, not included in the calculation. However, on the basis of certain characteristics of the right atrial pressure pulse, i.e., larve "v" waves and absence of "x" descent, this is considered to be applicable to only three animals.

The data in Figure 5 demonstrate significant and widely scattered deviations from normal of the relationship of ventricular work to end-diastolic pressure (EDP) during acute brisket disease. In every instance except one there was a reversion toward normal associated with recovery. According to the Starling concept of cardiac performance as modified by Sarnoff and Berglund (6), there are an infinite number or "family" of curves of this relationship. The curve of a normal heart is characterized by large increments in work for relatively small increases in EDP. Compromised ventricular function is characterized by progressively flatter curves which provide for less work output at progressively higher filling pressure. On this basis the changes noted in the relationship of work to EDP associated with recovery may be interpreted to be indicative of improvement in cardiac function. The possible exceptions to this are the two animals that showed high levels of right ventricular work (>7 kg-m per minute per m²) at only modest increases in EDP (<12 mm Hg) during acute brisket disease.

DISCUSSION

This study provides a dramatic demonstration of a remitting form of pulmonary vascular obstruction and of spontaneous recovery from heart failure. The uniformity and magnitude of decreases in pulmonary artery pressure and in calculated pulmonary vascular resistance leave little room for doubt that, coincident with recovery, substantial changes take place in the cross-sectional area of the vessels of major resistance in the lung. The relatively rapid reduction in *PVRI* associated with recovery coupled with the absence of pathologic evidence of consistent obstructive lesions (emboli or thrombi) in the pulmonary vessels of calves autopsied during acute brisket disease provides a strong argument for the presence of exaggerated vasomotor tone. Our pathologic findings, based on detailed gross and microscopic examination of the pulmonary vessels, are in accord with those observed by Alexander (7). If this conclusion is correct, pulmonary vasoconstriction associated with brisket disease represents in our minds the most striking example of this type of reaction to physiologic or pharmacologic stimuli.

The following evidence suggests that reduction in the oxygen tension of inspired (ambient) air attendant upon exposure to a high altitude is, indeed, the crucial stimulus for vasoconstriction. *1*) The present study demonstrates recovery among animals with brisket disease removed from the high altitude ranges to lower elevations. *2*) When animals with brisket disease are left (purposely or inadvertently) on the enzootic ranges, they invariably die. *3*) No evidence has been obtained (although searched for) to suggest that a factor or factors on the various ranges (or other geographic areas where the disease is enzootic) other than altitude are crucial determinants of the disease. *4*) To our knowledge, brisket disease in Utah has never been proven to occur in cattle herds maintained at altitudes below 7,000 feet. In fact, it has never been described to occur during the winter and spring in herds that are driven to the high ranges in early summer. *5*) The demonstration in a previous study that the exposure of normal calves to acute hypoxia (10 to 16% O_2) is associated with the development of significant elevation of pulmonary artery pressure and *PVRI* (8). Additional evidence that pulmonary vasoconstriction is consequent upon a hypoxic stimulus is provided by the study recently reported by Will, Alexander, Reeves, and Grover (9). These investigators convincingly demonstrated by serial cardiac catheterization studies that chronic exposure (6 months) of normal yearling calves to an altitude of 10,000 feet was associated with the development of moderate pulmonary hypertension in six animals and severe pulmonary hypertension in four. Two animals of the severe group developed manifestations characteristic of brisket disease. Pulmonary artery pressures remained constant during the same period of observation in ten control animals maintained at 5,000 feet on the same diet.

Although hypoxia is an important determinant of the development of this condition, apparently it is not the only one. The re-exposure of five animals in which susceptibility presumably was proved and the fact that of these only one had a recurrence leaves little doubt that some other factor or factors are involved. It is tempting to infer the operation in the four animals of some modifying influence associated with aging that prevents recurrence. Cattlemen long acquainted with this condition, however, have stated without equivocation that they have observed this condition in older animals that did not develop it during their initial exposure to altitude. The puzzle is far from being solved. The practical and logistic problems inherent in large, widely scattered herds owned by many individuals and distributed among several ranges where breeding is largely uncontrolled make an adequate genetic study an ambitious but unrealistic hope. That species differences may play a role is suggested by the fact that to our knowledge the disease has not been described in cattle of the species *Bos indicus* even though certain breeds of this species are native to altitudes as high as those mentioned here.

The observation made in the earlier report (2) and substantiated in the present study that pulmonary artery wedge and left ventricular filling pressures during acute brisket disease are more often elevated than not is potentially relevant to pathogenesis and deserves some comment.

It might be tempting to explain the development of pulmonary hypertension on the basis of an elevation of pressure in the pulmonary capillary-venous bed, thus invoking a mechanism analogous to that which has been proposed to explain pulmonary hypertension associated with mitral stenosis. On this basis, regression of pulmonary hypertension in brisket disease noted in the present study would depend primarily on lowering of left ventricular filling pressure. Again, this would be analogous to the situation that obtains in certain patients with mitral stenosis when the valvular obstruction is relieved surgically (10–12).

Evidence against the operation of such a mechanism in the etiology of pulmonary hypertension in brisket disease may be found in the studies of Will and co-workers (9) and Grover and Reeves

(13), as well as in observations of our own made in four animals. These have demonstrated significant pulmonary hypertension in the bovine in the absence of elevated pulmonary artery wedge or left ventricular diastolic pressures. Such observations suggest that the occurrence of left ventricular failure represents a secondary effect that augments pulmonary hypertension but is not the primary cause of it.

The demonstration of evidence of left ventricular failure (Figure 5) in many animals during acute brisket disease and its remission associated with recovery is of interest because the disease has been considered to be a form of cor pulmonale related primarily to pulmonary hypertension with consequent right ventricular hypertrophy and failure (2, 13, 15). It is beyond the scope of this presentation to consider the phenomenon of left ventricular failure, and it is dealt with in detail elsewhere (16).

The finding of an elevated pulmonary artery wedge pressure during acute brisket disease was initially considered to reflect the effects of left ventricular failure. Although this is true in the majority of instances, subsequent investigations have demonstrated that this is not invariably the case (17). It has also become feasible since the conclusion of this investigation to obtain direct measurements of left atrial pressure. The more precise data of the "true" pressure gradient across the pulmonary vasculature afforded by such measurements has in no significant way altered the conclusions reached with respect to the pathophysiology of brisket disease in this or previous studies.

This study provides a dramatic demonstration of the existence in nature of a spontaneously remitting physiologic derangement commonly encountered in clinical medicine, namely, pulmonary hypertension due to vascular obstruction. The information obtained, therefore, may have some bearing on such clinical disease states, as has been suggested (2, 18). There is, however, an implication of potentially greater clinical significance. It is that brisket disease may be considered to represent a naturally occurring, spontaneously remitting experimental model of heart failure. Accordingly, it provides a unique "preparation" in which it may be possible to study, both during and after recovery from congestive heart failure, a variety of physiologic, metabolic, or biochemical parameters that are or may be involved in this complex condition. Efforts along this line have been initiated (19).

SUMMARY

Hemodynamic observations were made on 14 calves that recovered from brisket disease (altitude-dependent, pulmonary, hypertensive heart disease in cattle). Data obtained are based on 43 venous and 21 left ventricular cardiac catheterization procedures carried out in these animals. Results of this study have demonstrated spontaneous remission of: *1*) all clinical manifestations of the disease, *2*) severe pulmonary hypertension (mean pulmonary artery pressure decreased from 63 ± 6 to 32 ± 3 mm Hg), *3*) elevated pulmonary vascular resistance (12.3 ± 2.2 to 3.8 ± 0.4 mm Hg per L per minute per m^2), and *4*) heart failure as manifest by pulmonary and systemic venous hypertension (mean right atrial pressure 21 ± 4 to 0.3 ± 1 mm Hg; mean pulmonary artery wedge pressure 23 ± 3 to 12 ± 3 mm Hg). Aggregate evidence strongly supports the hypothesis that pulmonary hypertension in brisket disease results from exaggerated hypoxic pulmonary vasoconstriction. However, determinants of the disease other than hypoxia remain to be elucidated. It is suggested that the natural occurrence of a spontaneously remitting form of heart failure provides a unique experimental model for further investigation.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the technical assistance of F. Ukradyha, R. P. Carlisle, and A. S. Ruby.

REFERENCES

1. Hecht, H. H., R. L. Lange, W. H. Carnes, H. Kuida, and J. T. Blake. Brisket disease. I. General aspects of pulmonary hypertensive heart disease in cattle. Trans. Ass. Amer. Phycns 1959, **72**, 157.
2. Hecht, H. H., H. Kuida, R. L. Lange, J. L. Thorne, and A. M. Brown. Brisket disease. II. Clinical features and hemodynamic observations in altitude-dependent right heart failure of cattle. Amer. J. Med. 1962, **32**, 171.
3. Kuida, H., A. M. Brown, R. L. Lange, and H. H. Hecht. Cardiovascular studies in normal calves. Amer. J. Physiol. 1961, **200**, 247.

4. Reeves, J. T., R. F. Grover, D. H. Will, and A. F. Alexander. Hemodynamics in normal cattle. Circulat. Res. 1962, **10**, 166.
5. Brody, S. Bioenergetics and Growth. New York, Reinhold, 1945, p. 403.
6. Sarnoff, S. J., and E. Berglund. Ventricular function. I. Starling's law of the heart studied by means of simultaneous right and left ventricular function curves in the dog. Circulation 1954, **9**, 706.
7. Alexander, A. F. The bovine lung: normal anatomy and vascular lesions in "high mountain disease of cattle." Proc. 5th ann. Conf. Res. Emphysema, Aspen, Colo., June, 1962. Med. thor. To be published.
8. Kuida, H., A. M. Brown, J. L. Thorne, R. L. Lange, and H. H. Hecht. Pulmonary vascular response to acute hypoxia in normal unanesthetized calves. Amer. J. Physiol. 1962, **203**, 391.
9. Will, D. H., A. F. Alexander, J. T. Reeves, and R. F. Grover. High altitude-induced pulmonary hypertension in normal cattle. Circulat. Res. 1962, **10**, 172.
10. Donald, K. W., J. M. Bishop, O. L. Wade, and P. N. Wormald. Cardio-respiratory function two years after mitral valvotomy. Clin. Sci. 1957, **16**, 325.
11. Semler, H. J., J. T. Shepard, and E. H. Wood. The role of vessel tone in maintaining pulmonary vascular resistance in patients with mitral stenosis. Circulation 1959, **19**, 386.
12. Likoff, W. The change in pulmonary vascular resistance after relief of mitral obstruction *in* Pulmonary Circulation, W. R. Adams and I. Veith, Eds. New York, Grune & Stratton, 1959, p. 302.
13. Grover, R. F., and J. T. Reeves. Experimental induction of pulmonary hypertension in normal steers at high altitude. Proc. 5th ann. Conf. Res. Emphysema, Aspen, Colo., June, 1962. Med. thor. To be published.
14. Alexander, A. F., and R. Jensen. Gross cardiac changes in cattle with high mountain (brisket) disease and in experimental cattle maintained at high altitude. Amer. J. vet. Res. 1959, **20**, 680.
15. Alexander, A. F., D. H. Will, R. F. Grover, and J. T. Reeves. Pulmonary hypertension and right ventricular hypertrophy in cattle at high altitude. Amer. J. vet. Res. 1960, **21**, 1.
16. Hecht, H. H., H. Kuida, and T. J. Tsagaris. Brisket disease. IV. Impairment of left ventricular function in a form of cor pulmonale. Trans. Ass. Amer. Phycns 1962, **75**, 263.
17. Kuida, H., T. J. Tsagaris, and H. H. Hecht. Evidence for pulmonary venoconstriction in brisket disease. Circulat. Res. 1963, **12**, 182.
18. Fishman, A. P. Respiratory gases in the regulation of the pulmonary circulation. Physiol. Rev. 1961, **41**, 214.
19. Kuida, H., T. J. Tsagaris, and H. H. Hecht. Starling's law of the heart in brisket disease (BD). Fed. Proc. 1962, **21**, 138.